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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/479,783	01/07/2000	STANLEY T CROOKE	ISIS-4313	3541

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EXAMINER

MCGARRY, SEAN

ART UNIT PAPER NUMBER

1635

DATE MAILED: 09/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/479,783

Applicant(s)

CROOKE, STANLEY T

Examiner

Sean R. McGarry

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 June 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 78-81, 93-98, 100-102, 106, 117-144, 146-156, 158, 165-168 and 170-181 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 78-81, 93-98, 100-102, 106, 117-144, 146-156, 158, 165-168, and 170-181 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/9/05 has been entered.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 78, 80, 81, 93-96, 98, 100-102, 117-144, 146, 153-156, 158, 165-168, 170-175, 180, 181 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has amended claims 78, 94, 95, 96, 98, 100-102, 121, 122, 127, 128, 133, 134, 139, 140, 146, 151, 152, 158, 170, 175, 180, and 181 to recite "wherein said first and second oligonucleotide comprises nucleotide sequence consisting from [eight/twelve/fifteen] to [fifty/thirty/twenty-five] nucleoside subunits."

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This language is unclear. The language could be interpreted in different ways and therefore renders the claims vague and indefinite. The metes and bound of the claimed invention are not clearly set forth. Applicant, in their response filed 6/09/05, asserts that the term "comprises" has been modified by the upper limit of the recited range. However the term "comprises" could be reasonably interpreted in its plain meaning to mean that the oligonucleotide of any length would contain an nucleotide sequence of any one of the members of the range. Looked at one way, one in the art could assert that the term "comprises" may be modified by the upper limit of the range if one adopts that the range is a description of one oligonucleotide of the invention, for exple. However one could reasonably assert that the range defines a genus of oligonucleotides of the invention. For example, one could reasonably interpret the claim to read "wherein said first and second oligonucleotide comprises nucleotide sequence consisting from 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or, 50 nucleoside units". The use of the term "comprises" in the context of the claim conflicts with the term "consisting" in the claim. The oligonucleotide comprises a sequence that consists of a certain length, but the oligonucleotide is not clearly limited to that length. The claim language, for example does not clearly limit an oligonucleotide of the invention that comprises a sequence that consists of 50 nucleoside subunits from containing one or more nucleotides. Since the oligonucleotide "comprises" the recited sequence, there is no limitation in the context of the claims that excludes the oligonucleotide from containing more nucleotides.

Claims 78-81, 93-98, 100-102, 106, 117-144, 146-156, 158, 165-168, and 170-181 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for the reasons of record.

The claimed invention is based on the substrate for a dsRNase from T24 cells. The structure of the dsRNase has not been disclosed. The claimed invention is drawn to a "double stranded RNA substrate". The scope of the claimed invention is vastly wider than a substrate for a particular dsRNase, for example. The specification, as filed describes particular 2' methoxy modifications with RNA gaps (See Figure 1, for example) that allowed the function of acting as a substrate for the RNase from T24 cells. The scope of substrates disclosed in the instant specification is therefore narrow. The claimed invention is drawn to dsRNA substrates with modifications that provide for increased hybridization and/or increased nuclease stability while allowing the dsRNA substrate to act as a "substrate". It is noted that no other substrate function other than the specific dsRNase substrate function has been disclosed in the instant specification. It is noted that the specification does not, for example, indicate any particular functional characteristics [substrate functions, for example] that are coupled with a known or disclosed correlation between function and structure. The specification does not disclose the structure of the specific dsRNase used to determine the functionality of the

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specific substrate disclosed in the instant specification for example. As is noted in the instant specification, RNase H is very sensitive to structural alterations in antisense oligonucleotides (see page 2, for example). There is no indication that dsRNases as a class would be non-effected by chemical modifications, for example. The instant invention, for example, reads on double stranded RNA substrates for any dsRNase protein. The instant specification provides no structure function relationship for any of these potential dsRNases and any particular modification that may or may not allow a dsRNA to function as a substrate for any particular dsRNase. Furthermore, it is not so clearly described what the function of substrate may be, for example. The instant specification describes a specific RNases that acts to cleave a substrate. The instant claims are not so limited but embraces any conceivable function of a substrate, for example. To satisfy the written description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563.

Applicant's arguments filed 6/09/05 have been fully considered but they are not persuasive. Applicant argues that since the claims no longer recite "substrate" the invention is now described. It is unclear how the amendment provides for a description of the invention since the disclosed invention of the application is in fact a double stranded RNA that is cleaved by a dsRNase. The asserted utility of the invention is the fact that a dsRNase III cleaves an oligonucleotide/target substrate. If applicant believes

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that there is another asserted utility or if a known art recognized utility exists such argument or evidence would be taken into consideration. The specification discloses single stranded RNA targeted to target RNAs to be cleaved by a dsRNase. At pages 93 it is disclosed double stranded RNAs that were used in cell lysates to detect dsRNase activity. The amendment fails to provide a description or provide a scope of the disclosed invention that has been adequately described. The scope of the invention has not been narrowed by the amendments but appears to have broadened the scope, for example (see applicants response, page 13, last sentence of third paragraph). For example, the amendments to the claims make it clear that the invention is now not limited to "RNA-like" oligomers as described in the specification as filed. The rejection is maintained for the reasons of record. Applicants' response fails to specifically address the reasons provided for finding a lack of adequate written description in the rejection of record.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 96, 98, 100, 142, 144, 146, 154, 156, 158, 166, and 168, and 170 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohtsuka et al [US 5,013,830, cited by applicant].

Ohtsuka et al have disclosed in Table 5 and the claims, for example double stranded oligonucleotides that comprise double stranded RNA portions. The compounds include one oligonucleotide that comprises both DNA and RNA portions. The RNA/DNA oligonucleotide hybridizes to an RNA oligonucleotide. Since RNA:RNA hybridizations are stronger than RNA:DNA hybridizations one can reasonably interpret such modification to be a modification that increases the affinity of an oligonucleotide [all DNA as opposed to RNS/DNA, for example] to a complementary oligoribonucleotide. The compound also includes the 2'-O-Me modifications which increase resistance to nucleases which are required by the instant claims. It is noted that the claims as amended do not require an RNA portion.

Applicant's arguments filed 6/09/05 have been fully considered but they are not persuasive. Applicant argues that the amendment to the claims drawn to "eight to fifty" and further range limitations render the invention novel since applicant asserts that the oligomer or Ohtsuka contains a strand of at least 90mer. It is noted that the claims

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require that the strands "comprise" sequences that consist of a range of nucleoside subunits. 90 comprises the ranges recited in the claims. Applicants arguments of the term "comprises" are not convincing and are addressed in the rejection under 37 CFR 112 second paragraph above.

Claims 78, 79, 94, 95, 99, 101, 102, 127, and 128 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Froehler et al [US 5,256,775, cited by applicant].

Froehler et al disclose RNA oligonucleotides (see column 4, for example) that are 3-50 nucleotides in length which contain modification on the 3' and 5' ends to protect from nucleases where the central portion of the oligonucleotide is phosphodiester linked (see column 5, for example). Since these oligonucleotides are disclosed for use to hybridize and inhibit an RNA target such as mRNA (see column 1 and 12, for example), the instantly claimed invention has been disclosed.

Froehler et al do not specifically provide the structure of a specific (ie a specific example) mRNA/oligonucleotide duplex, but do disclose at least a teaching of such structures at column 1 and 12, for example. It is the position of the examiner that such structures are anticipated by the disclosure at column 1 and 12, but nevertheless would be obvious since this is the specified reason for the oligonucleotides taught in the reference. One would clearly be motivated to make mRNA/oligonucleotide duplexes since it is in by the formation of those duplexes that a target mRNA is inhibited and such

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teachings would at the least make the invention as a whole prima facie obvious to one in the art at the time the invention was made.

Applicant's arguments filed 6/9/05 in regard to the Froehler reference have been fully considered but they are not persuasive moot in view of the new rejection above based on the Froehler reference.

Claims 78, 80, 81, 93-96, 98, 100-102, 117-122, 129-144, 146, 153-156, 158, 165-168, and 170-175 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. All of the above claims have been amended to or depend from claims that have been amended to read on double stranded oligomers where both strands comprise 8-50, 12-30, or 15-25 nucleotides. Applicant has pointed to page 7, lines 13-16 of the specification for support. Page 7 does indeed contain the words "about eight to about fifty" and "about twelve to about thirty" but not in the context now used. At page 7 of the specification the discussion is drawn to a single stranded RNA-like oligomer that is used to bind a target RNA. The target RNA is not discussed as being 8-50 or 12 to thirty or 15-25 nucleotides in length. The examiner

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was unable to find clearly apparent support for such a limitation in the context now used from the specification or claims as originally filed. If applicant believes that such support exists they are invited to point to such support with particularity.

Applicant's arguments filed 6/09/05 have been fully considered but they are not persuasive. Applicant relies on the generic definition of "complementary" to provide a basis for both strands of target comprising the recited ranges in the claims. Applicant asserts that the single stranded oligonucleotides described in the specification are not limited to being targeted to mRNA. Applicant then argues that if one takes the definition of complementary and with the disclosure and teaching of a single stranded oligonucleotide one in the art would find double stranded oligonucleotides comprising two of the single stranded oligonucleotides that have been taught in the specification. However, that the single stranded RNAs are for inhibiting a target RNA. It is unclear how one in the art would read the instant specification and be directed to make double stranded modified RNA-like oligonucleotides. What is one inhibiting? Why would one make complementary RNA-like oligonucleotides that are both modified within the size ranges disclosed in the specification when the specification teaches to use single stranded oligonucleotides to inhibit a target RNA? The specification fails to support such a construction within the context of the teaching of the single stranded RNA compounds. Applicant points to example 27 and Table I as evidence for the ranges. It is noted that the oligonucleotides of Example 27 and Table one are 17 mer dsRNAs that were used to detect the cleavage by an RNase III. Nowhere else in the specification is a

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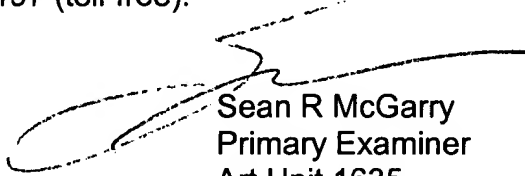
double stranded RNA disclosed. The Example relied on is not within the context of the asserted utility of the single stranded oligonucleotides taught in the specification. One in the art would not read the limitations or teachings of single stranded oligonucleotides that are taught for inhibiting a target RNA into a 17mer ds oligonucleotide that was taught only and specifically for the determination of whether a RNase was able to cleave double stranded RNA. The example shows that the dsoligonucleotides were used to test whether a dsRNase would cleave. The example is totally out of the context of the teachings of the specification for the modifications and size ranges for the single stranded RNA compounds described in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Sean R McGarry
Primary Examiner
Art Unit 1635